Pathogenesis of Photosensitivity in the Cutaneous Porphyrias

Henry W. Lim
Department of Dermatology, Henry Ford Hospital; Department of Pathology, Wayne State University School of Medicine, Detroit, Michigan, USA

The earliest well-documented case of porphyria is that of King George III of England. In 1811, he was described to have abdominal pain, tachycardia, discolored urine, and "madness". He was permanently affected by this condition from 1811 until his death in 1820. Between 1911 and 1983, all the known types of porphyria were described (Nordmann *et al*, 1983; Mascaro and Lim, 2000). Because of the presence of phototoxic porphyrins, all cutaneous porphyrias are associated with photosensitivity. The non-cutaneous porphyrias, 5-aminolevulinic acid (ALA) dehydratase deficiency porphyria and acute intermittent porphyria, do not have cutaneous findings. This is due to the fact that the defective enzymes in these two types of porphyria, ALA dehydratase and porphobilinogn deaminase, respectively, are enzymes that appear early in the heme biosynthic pathway; therefore, the substrates for these enzymes are non-phototoxic porphyrin precursors.

Erythropoietic protoporphyria (EPP) was first described by Professor Ian Magnus, a photodermatologist at St John's Institute of Dermatology in London in 1961 (Magnus *et al*, 1961). His patient had pain following sun exposure; protoporphyrin was present in his erythrocytes and bone marrow. The action spectrum of induction of lesions on the skin was in the Soret band region (400–410 nm), consistent with the absorption spectrum of protoporphyrin. Since this original description, EPP has been reported from around the world. It is the second most common type of cutaneous porphyria after porphyria cutanea tarda (PCT). It is now known that the abnormal porphyrin profile seen in EPP is due to defective ferrochelatase, the last enzyme in the heme biosynthetic pathway. Ferrochelatase catalyzes the insertion of ferrous iron into protoporphyrin IX to form heme. The cDNA encoding this enzyme has been cloned, and the gene has been mapped to chromosome 18q22 (Nakahashi *et al*, 1990; Whitcombe *et al*, 1991).

EPP usually manifests itself in childhood. Patients complain of burning and stinging sensations upon exposure to sunlight, frequently associated with cutaneous edema. With repeated exposure, purpura of the exposed areas, most commonly dorsum of hands and forearms, and waxy thickening of the knuckles and metacarpophalangeal and interphalangeal joints can occur. Shallow, pitted scars occur on frequently sun-exposed areas, especially the forehead and nose bridge. Vesicles, erosion, and crusting are observed only rarely, usually following extensive sun exposure. As with many other photodermatoses, EPP tends to be active in the spring and summer months, and well controlled during the winter.

There are several factors that contribute to the development of cutaneous lesions in EPP. Protoporphyrin, upon exposure to Soret band radiation, is known to generate reactive oxygen species, which in turn could result in lipid peroxidation of the cell membranes, resulting in the lysis of cells (Goldstein and Harber, 1972). Using purified mast cells as a model, it has been demonstrated that protoporphyrin and Soret band radiation induce the release of mast cell-derived mediators; this process could be downregulated by the presence of catalase, which inactivates hydrogen peroxide (Lim *et al*, 1987). In patients with EPP, there is thickening of the capillary endothelial cell walls, manifested by positive periodic acid-Schiff staining. Exposure to Soret band radiation has been shown to result in lysis of the endothelial cells (Schnait *et al*, 1975). Electromicroscopic examination showed that the thickened endothelial cell wall consisted of multiple layering of the basal lamina of the endothelial cells. In a protoporphyric mouse model, it has been demonstrated that the chronic exposure to Soret band radiation resulted in repeated lysis of the endothelial cells, with intact basal lamina. Upon regeneration of these cells, multiple layering of basal lamina would then take place (Hönigsmann *et al*, 1976). β-carotene, a commonly used therapeutic modality for the management of patients with EPP during the summer months, is a quencher of oxygen-free radicals. Its therapeutic efficacy in EPP, reported in some studies, is supportive evidence for the role of reactive oxygen species in the pathogenesis of cutaneous lesions in this condition (Mathews-Roth *et al*, 1974).

Inflammatory cells and soluble mediators of inflammation have also been shown to play a role in this process. *In vitro*, protoporphyrin and Soret band radiation could induce the release of mast cell-derived mediators (Lim *et al*, 1987). It should be noted that this process does not occur when uroporphyrin is used. This is probably a reflection of the physical and chemical properties of these two types of porphyrins. Protoporphyrin is a 2-carboxyl porphyrin, which is lipophilic; in contrast, the 8-carboxyl uroporphyrin is a hydrophilic porphyrin. This may explain the differences in the clinical manifestations of patients with EPP, in which protoporphryin is the predominant elevated porphyrin, and those of patients with PCT, in which uroporphyrin is the predominant porphyrin. Patients with EPP present with cutaneous erythema, urticarial lesions, and edema, where mast cell-derived mediators might play a significant contributory role. The lack of direct effect of uroporphyrin on

Abbreviations: EPP, erythropoietic protoporphyria; PCT, porphyria cutanea tarda

mast cells may partly explain the manifestations of PCT, in which patients present with skin fragility and bulla formation, without erythema and edema. The differences between the physical and chemical properties of protoporphyrin and uroporphyrin also explain the differences in the urinary porphyrin profile of these two types of porphyrias. In EPP, urinary porphyrin is negative. In contrast, in PCT, hydrophilic uroporphyrin and 7-carboxyl porphyrin are routinely elevated in the urine.

In an animal model, polymorphonucler cells have also been known to play a role in porphyrin-induced phototoxicity. In leukopenic animals, the phototoxic response was suppressed (Lim *et al*, 1985). The complement system is another mediator of inflammation that has been shown to play a pathogenic role. In the presence of either protoporphyrin or uroporphyrin, *in vitro* exposure to Soret band radiation resulted in the activation of the complement system, and the generation of anaphylatoxins (Lim and Gigli, 1981; Lim *et al*, 1981). *In vivo* exposure to Soret band radiation of skin of patients with EPP and PCT also resulted in the generation of anaphylatoxins (Lim *et al*, 1984).

The role of mast cells, leukocytes and the complement system have been explored in detail in animal models. Porphyrin-induced phototoxicity was associated with an increase in serum histamine levels (He *et al*, 1989); the phototoxic response was suppressed in skin sites where mast cells had been degranulated by interdermal injection of compound 48/80 performed prior to irradiation (Lim *et al*, 1985). Leukopenic animals, complement-depleted animals, and animals congenitally deficient of the fifth component of complement had markedly diminished porphyrin-induced phototoxicity (Lim *et al*, 1981, 1985).

In vitro, increased synthesis of collagen by fibroblasts has been reported following incubation with uroporphyrin; this occurred in the absences of radiation (Varigos *et al*, 1982). This observation may serve as a partial explanation for the development of sclerodermoid skin changes observed in some patients with PCT; it is well recognized that these sclerodermoid changes occur both in sun-exposed as well as sun-protected areas of the skin.

In the current issue of the JID, Pawliuk *et al* (2004) elegantly demonstrated that elevated erythrocyte and plasma protoporphyrin levels alone are not sufficient to induce the development of cutaneous lesions in mice. The authors transplanted bone marrow from BALB/C-Fech^{mlPas} mice, an EPP mouse model, to normal recipients. They demonstrated that although the recepients developed markedly elevated levels of protoporphyrin in the erythrocytes as well as in the plasma, these animals did not develop cutaneous photosensitivity, nor did they develop any evidence of hepatic damage. The authors suggest that the normal dermal and hepatic ferrochelatase levels prevented the development of these changes. To confirm this hypothesis, they were able to demonstrate that photosensitivity did not develop in skin transplanted from normal mice to the back of EPP mice. These findings not only increase our understanding of the pathophysiology of cutaneous lesions EPP, they also provide a foundation for potential therapy. Topical delivery of the defective enzyme, ferrochelatase, could potentially restore the enzymatic activity in the dermis of EPP patients, hence minimizing their phototoxicity. The success of this therapeutic strategy would usher in a new and exciting era for patients with EPP and those with other types of cutaneous porphyrias, and for all of us who care for these patients.

DOI: 10.1111/j.0022-202X.2004.23531.x

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